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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/595, 7/16 — A1

(11) International Publication Number: WO 92/18133

(43) International Publication Date: 29 October 1992 (29.10.92)

(21) International Application Number: PCT/US92/02806

(22) International Filing Date: 10 April 1992 (10.04.92)

(30) Priority data:
683,380 — 11 April 1991 (11.04.91) — US
802,646 — 9 December 1991 (09.12.91) — US

(60) Parent Applications or Grants
(63) Related by Continuation
US — 683,380 (CIP)
Filed on — 11 April 1991 (11.04.91)
US — 802,646 (CIP)
Filed on — 9 December 1991 (09.12.91)

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(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US .

Published
With international search report.

(54) Title: METHOD OF TREATMENT USING STEROID MOUTHWASH

(57) Abstract

The object of the present invention is to provide a means of treating patients suffering from inflammatory conditions of the mouth using aqueous anti-inflammatory steroids in solutions that can be swished and expectorated as a mouthwash. Such therapy would allow direct contact of the medication with the diseased mucous membranes and would contact areas of the oral cavity that would not usually be reached with application of creams, gels, or ointments. Swishing for three to five minutes, then expectorating the aqueous anti-inflammatory-containing, results in maintenance of contact of the active agents with the oral cavity surfaces for a longer time than would application of gels containing those agents. The mode of application is simple and is not repugnant to the patient as is the application of creams, gels or ointments.

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METHOD OF TREATMENT USING STEROID MOUTHWASH

Field of the Invention:

The invention is related to treatment of inflammatory diseases of the mouth using anti-inflammatory steroids in combination with antifungal drugs in an aqueous medium as a mouthwash.

Background of the Invention:

The treatment of inflammatory diseases of the mouth is difficult. Patients so afflicted often require treatment with agents that are potentially toxic when given systemically to control the disease activity. Moreover, diseases such as oral lichen planus, pemphigus, pemphigoid, aphthous stomatitis, erythema multiforme, and idiopathic stomatitis are disorders in which spontaneous remissions are rare. Means of treating such diseases without undue exposure of the patient to systemic effects of powerful therapeutic agents is desirable.

Treatment with topical corticosteroids as presently formulated and administered has significant limitations. Existing commercially available compositions are usually supplied as creams, gels, or ointments that are intended for cutaneous applications. Such preparations are not readily acceptable to patients for use on the mucosa. The prior art compositions must be applied frequently (up to six times a day). Furthermore, the compositions are not readily applied to the areas of the oral cavity that are difficult to reach. Furthermore, treatment with steroids causes increased susceptibility to fungal infections of the mouth. This complication is especially common in patients suffering from oral lichen planus, a condition in which Candida is found to colonize mouth lesions in 25% of the patients.

Aqueous solutions of steroids have been known. Kena-

log (TM) 10 Injection is an aqueous suspension used for intradermal, intra-articular, and intrabursal administration. The suspension is not appropriate for use intravenously or intramuscularly, and there is no suggestion that the suspension can be used as a mouthwash or swish for treatment of inflammatory diseases of the oral cavity. Aristospan (TM) is also used as a suspension for intralesional administration and is available as a cream for topical application. Similarly, Kenalog-H (TM) cream is applied topically to the skin. All of these preparations have, as an untoward effect, an increased susceptibility to fungal infections. A preparation containing an antifungal, nystatin, and a steroid, triamcinolone acetonide, is provided as a cream under the trade name Mycolog II. It is not appropriate for use as a mouthwash. A preparation containing nystatin for use as a swish (mouthwash) has been available. However, that preparation does not contain any anti-inflammatory steroid as an active agent.

In the patent literature, no teaching of use of mouthwashes containing both antifungal agents and anti-inflammatory agents has been found. Segel, et al, in U.K. Patent Application GB 2,167,296 A describes pharmaceutical compositions containing glycyrrhizin for topical application. That patent publication indicates that the glycyrrhizin, a necessary component of the compositions taught therein, formed stable gels. The compositions taught therein would not be considered useful as mouthwashes. United States Patent 4,101,652 to Bonati teaches complexes of saponins with sterols for use in treating inflammation. The complex having a saponin as an essential moiety is necessary to that invention. No teaching of preparations for use as mouthwashes is seen therein. United States Patent 4,933,172 to Clark, et al. teaches the nonsteroidal anti-inflammatory agent 2-(2,6 Dichloro-3 methylphenylamino) benzoic acid for use in treating gingivitis. One of the formulations taught is a mouthwash. United States Patent 4,835,142 to Sazuki, et al. describes powdery compositions

for application to the mucosa of the oral or nasal cavity. United States Patent 4,782,047 to Benjamin, et al. teaches use of anti-inflammatory steroids as nasal sprays. No method for treating oral infections using mouthwashes is disclosed therein.

R. A. Cawson ("Treatment of Oral Lichen Planus with Betamethasone", British Medical Journal, (January 13, 1968)) teaches the use of betamethasone pellets to treat oral lichen planus. Use of hydrocortisone pellets was also tried. The betamethasone pellets were efficacious. Hydrocortisone pellets were also tried but were rarely effective, even when combined with tetracycline mouthwashes.

Rothwell and Spektor ("Palliation of Radiation-related Mucositis", Special Care in Dentistry, (January-February 1990)) discloses method of treating patients undergoing irradiation therapy comprising prophylactic use of mouth rinse with a solution containing tetracycline, 500 mg; nystatin, 1,200,000 U; hydrocortisone, 100 mg; and diphenhydramine elixir, 10 ml. to make a solution of 25 ml. It is taught that tetracycline is unstable in solution and was, therefore, dispensed as a separate solution. It is not clear if the tetracycline was mixed with the other active agents just before using the rinse. However, the method taught therein was not used to treat existing, chronic inflammatory problems such as oral lichen planus.

Summary of the Invention:

The object of the present invention is to provide a means of treating patients suffering from inflammatory conditions of the mouth using aqueous anti-inflammatory steroids in solutions that can be swished and expectorated as a mouthwash. Such therapy would allow direct contact of the medication with the diseased mucous membranes and would contact areas of the oral cavity that would not usually be reached with application of creams, gels, or ointments.

It is also an object of the invention to provide a method of treating patients suffering from inflammatory

conditions f the oral cavity using compositions containing both anti-inflammatory steroids and antifungal agents in solutions that can be swished and expectorated. The combination of active agents would alleviate the inflammatory condition while inhibiting the growth of Candida species. The use of such mouthwashes would result in efficient application of both agents to all of the surfaces of the oral cavity, including areas that would not be readily reached by application of gels, creams, or ointments.

Swishing for three to five minutes, then expectorating the aqueous anti-inflammatory-containing, results in maintenance of contact of the active agents with the oral cavity surfaces for a longer time than would application of gels containing those agents. The mode of application is simple and is not repugnant to the patient as is the application of creams, gels, or ointments.

Detailed Description of the Invention:

It is now possible, using the methods of the invention, to provide treatment to patients suffering from inflammatory conditions of the mouth in a manner that is effective, efficient, and results in minimal undesirable side effects. It has been found that patients suffering from such conditions may be treated using solutions of steroids as a mouthwash. Preferred mouthwashes contain, in addition to the steroids, antifungal agents. Treatment using the method of the invention is far more acceptable to patients than the use of creams, gels, or ointments. Furthermore, treatment using a mouthwash as a swish results in far better exposure of the entire oral cavity to the active agents.

The compositions used as mouthwashes preferably should be in the acidic range since most of the steroids and antifungal agents are more soluble in acidic solutions. A pH of 3.5 to 7 is desirable, with a pH of 4 to 6.5 being more preferable. A solution having a pH of less than 4 would be likely to cause a stinging sensation. Steroids and anti-

fungal agents are usually less soluble at pH higher than 7. Furthermore, at higher pH the solutions are often unpleasant to use.

Anti-inflammatory steroids are classified according to anti-inflammatory efficacy of the preparation or according to relative effectiveness of the particular active agent used. (i.e., How much active agent is required to obtain a given effect?) Cornell and Soughton, assigning efficacy to each preparation, assign a low efficacy to some preparations of hydrocortisone. A second method of classification ranking relative anti-inflammatory potency ranks anti-inflammatory agents in relation to the amount of agent needed to obtain a given anti-inflammatory effect wherein the more effective agents having a higher number assigned with a ranking of one given to hydrocortisone. Hydrocortisone at a ranking of 1 and is listed as requiring an approximate dosage of 20 mg. while prednisolone, which provides equivalent anti-inflammatory effect using a dosage of 5 mg. is assigned a relative anti-inflammatory potency of 4 and betamethasone, with .75 mg. required to obtain equivalent anti-inflammatory effect, is assigned a relative anti-inflammatory potency rating of 25. (See Goodman and Gillman, The Pharmacological Basis of Therapeutics, (Eighth Ed.), Pergamon Press, New York (1990) p 1447.) Using the ranking of relative anti-inflammatory effect in relation to hydrocortisone described above, any agent having a relative anti-inflammatory effect in relation to hydrocortisone of 2.5 or above would be deemed useful for the practice of the invention. More preferred anti-inflammatory agents would be those having a relative anti-inflammatory effect of at least 5.

Other factors to be considered in choosing a particular anti-inflammatory agent include cost and absorption of the particular agent would be important factors in selecting the particular steroid. Steroids particularly suggested for use in the method of the invention are triamcinolone and derivatives (particularly diacetate, hexacetonide, and

acetonide), betamethasone and its derivatives (including particularly the dipropionate, benzoate, sodium phosphate, acetate, and valerate), flunisolide, prednisone and its derivatives, fluocinolone and its derivatives (particularly the acetonide), diflorasone and derivatives (particularly the diacetate), halcinonide, desoximetasone, clobetasol (especially the propionate), alclometasone, fluticasone (particularly the propionate) and desonide. The effective concentration of drug will vary with the active agent used. Concentration would fall within the 0.01% to 1% range. For example, for betamethasone and its derivatives the preferred concentration would be 0.01% to 0.2% while the preferred concentration of triamcinolones would be 0.025% to 1%.

The preferred antifungal agents used in the method of the invention show great effectiveness against Candida species and are poorly absorbed from the mucosa of the intestinal tract. Some preferred antifungal agents are nystatin, clotrimazole, econazole, oxiconazole, ketoconazole, miconazole, ciclopirax olamine, amphotericin B, and sulconazole, all of which are poorly absorbed from the intestinal tract. Nystatin and clotrimazole are particularly preferred agents.

In addition to anti-inflammatory and antifungal agents, the aqueous solution may contain buffers, surfactants, humectants, preservatives, flavorings, stabilizers (including antioxidants) colorants, and other additives used in solutions administered into the oral cavity. Of course other medicinal agents may be added for purposes of alleviating other undesirable conditions in the mouth. Such agents could include, for example, analgesics, antibacterial agents, and emollients.

Some of the appropriate buffer systems for use in practice of the invention include citric acid-citrate salts, acetic acid-acetate salts, and benzoic acid-benzoic salt systems. However, any buffer system commonly used for preparing medicinal c mpositi ns would be appropriate.

Flavorings used in the dentifrice art such as peppermint, citrus flavorings, berry flavorings, vanilla, cinnamon, and sweeteners, either natural or artificial, could be used in compositions of the invention.

While the vehicle used generally is primarily water, other vehicles may be present such as alcohols, glycols (polyethylene glycol or polypropylene glycol are examples), glycerin, and the like may be used to solubilize the active agents. Surfactants may include anionic, nonionic, amphoteric and cationic surfactants which are known in the art as appropriate ingredients for mouthwashes.

Suitable preservatives include, but are not limited to, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), benzoic acid, and ascorbic acid.

EXAMPLE 1:

Preparations:

A buffered solution containing benzalkonium chloride 0.02%, and 0.1% benzoic acid in water is adjusted to pH 4.5 with sodium benzoate. Betamethasone dipropionate and nystatin are added in sufficient quantities to provide a composition having a concentration of active agents in excess of 0.05% of betamethasone dipropionate and 100,000 units nystatin per ml. The pH is again adjusted to 4.5 and sufficient buffered solution added to provide a composition having 0.05% betamethasone dipropionate and nystatin 100,000 units per ml. (A dose for swishing is 5 ml.)

The solution is supplied in sealed containers containing 5 ml. The patient is instructed to use one container full three times daily at least three hours before the next meal. Before use, the teeth should be cleaned and the mouth rinsed. The solution is to be swished around in the mouth for at least 3 minutes, then expectorated. Nothing is to be taken by mouth for at least 30 minutes after use of the mouth wash.

EXAMPLE 2:

A composition is prepared in the manner disclosed in Example 1. The active anti-inflammatory agent used is triamcinolone added in an amount to provide a final product having triamcinolone 0.1% and nystatin 100,000 units per ml. The composition is packaged in individual doses of 5 ml. in sealed containers. Instructions for use are the same as those for the composition of Example 1.

Example 3:

A mouthwash is prepared as indicated in Example 1. However, the preparation is packaged in a bottle containing multiple doses. The patient is instructed to use one teaspoon of fluid three times daily at least three hours before the next meal. Before use, the teeth should be cleaned and the mouth rinsed. The solution is to be swished around in the mouth for at least 3 minutes, then expectorated. Nothing is to be taken by mouth for at least 30 minutes after use of the mouthwash.

Example 4:

A mouthwash composition is prepared by the method used in Example 1 except that the active agents are replaced with clobetasol propionate 0.05% as the anti-inflammatory steroid and, as the antifungal agent, oxiconazole nitrate 1%.

Example 5:

A mouthwash composition is prepared by the method of Example 1 except that the active agents are replaced with the steroid alclometasone dipropionate 0.05% and, as the antifungal agent, oxiconazole nitrate 1%.

Example 6:

A mouthwash composition is prepared by the method of Example 1 except that the active agents are replaced with the steroid fluticasone propionate 0.05%.

Exampl 7:

A mouthwash composition is prepared by the method of Example 2 except that the concentration of triamcinolone is .5%. Nystatin dosage is still 100,000 U/ml.

Example 8:

A mouthwash composition is prepared in accord with the method of Example 1 except that the antifungal agent was clotrimazole 1%.

Comparative Data:

The mouth washes of the invention were compared for effectiveness with known commercial formulations. Each of the patients were first treated with the known formulations. In the patients tested, response to the prior art compositions was poor.

Patient #1 Diagnosis: Lichen planus

Patient #2 Diagnosis: Pemphigoid

Drug	Response (Pt.#1/Pt.#2)
Mycolog II:	±/0
Lotrasone:	+/+
Mouthwash of Example 2:	++/+++
Mouthwash of Example 7:	++++/++++
Mouthwash of Example 8:	++++/++++

0: no improvement, +: slight improvement, ++: moderate improvement, +++: good improvement, ++++: excellent improvement.

As indicated above, the use of the swish in accord with the teachings of the specification provides greatly increased therapeutic relief in the treatment of the cited inflammatory conditions of the mouth. Hence, it can be

seen that the use of the liquid mouthwash preparation as described provides substantial benefit over the commercial products of the art. While several useful anti-inflammatory compositions have been exemplified, it is understood that other anti-inflammatory steroids could be chosen from among those having a potency of ≥2.5 in relation to hydrocortisone and other antifungal agents, especially those that are poorly absorbed in the gastrointestinal tract, could be used in accord with the teachings of this disclosure without departing from the spirit of the invention.

The compositions of the invention containing anti-inflammatory agents and antifungal agents can be used for veterinary purposes as well. However, when so used the therapeutic compositon would be sprayed into the oral cavity after the teeth of the animal have been cleaned. The animal would then be prevented from ingestion of food or water for about 30 minutes

As would be obvious to one of ordinary skill in the art, other additives, including other active agents, could be incorporated with the active agents of the invention as taught herein.

Claims:

1. A composition of matter comprising a liquid aqueous solution containing as active agents an antifungal effective amount of at least one antifungal agent and anti-inflammatory effective amount of at least one anti-inflammatory steroid having a relative anti-inflammatory potency of at least 2.5 when compared to hydrocortisone.

2. A composition of claim 1 having a pH of 3.5 to 7.

3. A composition of claim 2 having a pH of 4 to 6.5.

4. A composition of claim 3 wherein the anti-inflammatory steroid is selected from the group consisting of triamcinolone or a derivative thereof, betamethasone or a derivative thereof, flunisolide, prednisone or a derivative thereof, fluocinolone or a derivative thereof, diflorasone or a derivative thereof, halcinonide, desoximetasone, clobetasol, alclometasone, fluticasone, and desonide.

5. A composition of claim 1 wherein the fungicidal antifungal agent is selected from the group consisting of nystatin, clotrimazole, econazole, oxiconazole, ketoconazole, miconazole, ciclopirax olamine, amphotericin B, and sulconazole.

6. A composition of claim 5 wherein the anti-inflammatory steroid is betamethasone dipropionate.

7. A composition of claim 5 wherein the anti-inflammatory steroid is triamcinolone.

8. A composition of claim 5 wherein the anti-inflammatory steroid is clobetasol propionate.

9. A comp sition of claim 5 wherein the anti-inflammatory steroid is alclometasone dipropionate.

10. A composition of claim 5 wherein the anti-inflammatory steroid is fluticasone propionate.

11. A composition of claim 1 wherein the antifungal agent is nystatin.

12. A composition of claim 1 wherein the antifungal agent is oxiconazole.

13. A composition of claim 1 wherein the antifungal agent is clotrimazole.

14. A composition of claim 4 wherein the antifungal agent is nystatin.

15. A composition of claim 4 wherein the antifungal agent is oxiconazole.

16. A composition of claim 4 wherein the antifungal agent is clotrimazole.

17. A composition of claim 5 wherein the steroid is triamcinolone.

18. A composition of claim 5 wherein the steroid is betamethasone dipropionate.

20. A composition of claim 5 wherein the steroid is clobetasol propionate.

21. A composition of claim 5 wherein the steroid is alclometasone dipropionate.

22. A composition of claim 5 wherein the steroid is fluticasone propionate.

23. A method of treating inflammatory conditions of the mouth comprising the steps of:
(1) swishing a mouthwash composition containing as an active agent an anti-inflammatory effective amount of an anti-inflammatory steroid having a potency of at least 2.5 when compared to hydrocortisone in an aqueous medium around in the mouth to allow all of the oral lining to be reached by the solution and;
(2) expectorating the solution.

24. A method of claim 23 wherein the composition used in step 1 also contains an antifungal effective amount of an antifungal agent.

25. A method of claim 24 wherein the antifungal agent is selected from the group consisting of nystatin, clotrimazole, econazole, oxiconazole, ketoconazole, miconazole, ciclopirax olamine, amphotericin B, and sulconazole.

26. A method of claim 23 wherein the steroid is selected from the group consisting of triamcinolone or a derivative thereof, betamethasone or a derivative thereof, flunisolide, prednisone or a derivative thereof, fluocinolone or a derivative thereof, diflorasone or a derivative thereof, halcinonide, desoximetasone, clobetasol, alclometasone, fluticasone and desonide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/02806

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/595; A61K 7/16
US CL :514/171; 424/49
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/171; 424/49

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Special Care in Dentistry, January-February 1990, Rothwell, Palliation of radiation-related mucositis, pages 21-25, see entire document.	1-26
Y	Merck Index, 1976, pages 309,310,875,876, see entire 623,2370,6547	1,5,11,13, 14,23-25
Y	Chemical Engineer's Handbook, 1973, Perry, page 22-52, see entire page.	1-3,23
Y, P	Facts and Comparisons, 1992, see entire document.	1-26
Y	US Pharmacopeia, The National Formulary. 1980, see entire document.	1-26
Y	Remingtons 17, 1985, see entire document	1-26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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